degenerated liver and being deficient in T and B cells; and

b. repopulating the parenchyma of the degenerated liver by transplanting xenogenic mammalian hepatocytes that are a natural host for infection with one or more compatible hepatitis virus into said liver.

38. A chimeric mouse model system for hepatitis comprising an immunetolerant mouse deficient in T and B cells having a degenerated liver parenchyma repopulated with transplanted xenogenic mammalian hepatocytes that are a natural host for infection with one or more compatible hepatitis virus.

REMARKS

Reconsideration of this application is respectfully requested in view of the above amendments and the following remarks,.

I. Status of the Claims and Specification

By this amendment, claims 1-38 are pending. Claims 1, 8, 14, 15, 23, 25 and 35 have been amended. Claims 37 and 38 have been added.

Claims 1, 8, 15 and 25 have been amended to recite an immunetolerant mouse deficient in T and B cells. Support for these amendments is found in the specification at page 7, line 36 through page 8, line 1.

Applicants represent for the record that claims 1, 8, 15 and 25 do not represent the broadest embodiment of the invention. The instant invention also encompasses, for example, embodiments wherein a transgenic immunetolerant mouse deficient in B cells and T cells with

degenerated liver is repopulated with xenogenic mammalian hepatocytes that are a natural host for a compatible hepatitis virus, but which hepatocytes âre not in fact infected by a hepatitis virus. New claims 38 and 39 are drawn to this embodiment of the invention.

Claims 14, 23 and 35 have been amended to recite that the source of xenogenic mammalian hepatocytes is a woodchuck. Support for these amendments is found in the specification at page 8, lines 25-30.

New claims 38 and 39 are supported by claims 1 and 8 of the application as filed. Further support for repopulating degenerated liver parenchyma with hepatocytes that are a "natural host" for infection by hepatitis virus is found in the specification, e.g., at page 3, lines 16-20; page 4, lines 21-24; page 9, Table 1; and page 11, lines 14-17.

All new and amended claims are supported by the application as filed. No new matter has been added to the application.

II. Oath/Declaration

A substitute Declaration, duly executed by the inventors, is enclosed.

III. Rejections Under 35 U.S.C. §112, First Paragraph

Claims 1-36 stand rejected under 35 U.S.C. §112, first paragraph. The Examiner alleges that the specification does not enable one of ordinary skill in the art to practice the full scope of the claims. The bases of the Examiner's rejection of the claims are addressed as follows:

(i) The Examiner contends that it is unpredictable as to which immunetolerant mice are operative as claimed. In response, claims 1, 8, 15 and 25 have been amended and are

now directed to an "immunetolerant mouse deficient in T and B cells". One of ordinary skill in the art would find it predictable that any immunetolerant mouse deficient in T and B cells could receive transplanted xenogenic hepatocytes capable of being infected with a compatible virus. Examples of such mice, i.e., RAG1 and RAG2 knockout mice and SCID mice, are given in the specification at page 8, lines 1-3. Nude mice are excluded from the present list due to the presence of B cells.

The Examiner further contends that "immunetolerant mice" can encompass mice with even a "slightly suppressed" immune system, such as a mouse with a cold. The amended claims are not drawn a mouse comprising a "suppressed" immune system, but rather to an "immunetolerant mouse deficient in B and T cells". Given the definition of immunetolerant and the examples of immunetolerant mice set forth in the specification, each of which is severely immunodeficient, one of ordinary skill in the art would not find it reasonable to define a mouse with a slightly suppressed immune system or a mouse with a cold, to use the Examiner's example, as an "immunetolerant mouse deficient in T and B cells". One of ordinary skill in the art would not entertain the notion that a mouse with a cold could or should serve as the claimed recipient for xenogenic transplants.

With further regard to the immunetolerant mice encompassed by the amended claims, the Examiner cites Baumgardner et al.'s (Immunol. Rev., 174:260-279, 2000) disclosure that CD4 knockout, CD8 knockouts, B-cell knockouts, MHCII knockouts, CD4+ reconstituted SCID mice and CD8+ reconstituted SCID mice all reject transplanted liver tissue. Applicants respond by noting that each these mice contain either B or T cells. None of the mice disclosed in Baumgardner are deficient in both B and T cells. Accordingly, none of the mice disclosed in

Baumgardner is encompassed by the claims.

Finally, the Examiner contends that it is not predictable if the claimed immunetolerant mice can be infected with a compatible hepatitis virus, because both the humoral and cellular immune responses are important for viral clearance. Applicants respond that the amended claims are directed to an immunetolerant mouse deficient in T cells and B cells. Such an immunetolerant mouse is deficient in both humoral and cellular immune responses.

In summary, Applicants respectfully submit that the specification is enabling for the full scope encompassed by an "immunetolerant mouse deficient in T cells and B cells".

(ii) The Examiner continues to allege that the specification is enabling only for transplanting xenogenic hepatocytes into an immunetolerant mouse in which liver degeneration is caused by the homozygous uPA transgene.

The Examiner asserts that the invention cannot be practiced with a uPA hemizygous mouse. Applicants respectfully traverse on the grounds that the specification discloses that both hemizygous and homozygous uPA mice were used in the embodiments disclosed in the examples (see specification at page 17, lines 6-7). Furthermore, all experiments disclosed in Petersen et al. (Proc. Natl. Acad. Sci. USA 95:310-315, 1998), upon which much of the present application is based, were performed with hemizygous uPA mice (see Petersen et al., page 311, under "Generation of Tolerant uPA/RAG-2 Mice"). Accordingly, notwithstanding the Examiner's inference based upon Rhim et al., the invention defined by the present claims may be practiced with either a homozygous or hemizygous uPA mouse.

In further support of the scope of the claims, Applicants have previously submitted references showing that, in addition to expression of a uPA transgene, other methods

of creating degenerated liver were known in the art at the time the invention was made. (*See* Overturf et al., Nature Genetics, 12:266-273, 1996 and Laconi et al., American Journal of Pathology, 153:319-329, July 1, 1998).

The Examiner alleges, however, that other methods of liver degeneration, such as administration of liver toxic chemicals would kill both host hepatocytes and donated hepatocytes and would allow competition between host and transplanted hepatocytes. The references already of record in this application indicate that this position would not be correct.

Laconi et al. disclose that differential effects of a toxic chemical on host hepatocytes versus donated hepatocytes may be accomplished simply by discontinuing chemical treatment prior to transplanting donor hepatocytes (see Laconi et al., page 320 under "Animals, Diets and Cell Transplantation Protocols"). Laconi et al. disclose further that at two months post-transplantation, the level of hepatocyte replacement in treated female animals is 40-60% and in male animals is 90-95%. These numbers are stable through at least nine months post-transplantation (see Abstract).

Overturf et al. also disclose methods for effecting liver degeneration in a host, then repopulating liver with donor hepatocytes that have a growth advantage over host hepatocytes. In the methods of Overturf et al., liver degeneration in host mice is caused by a genetic defect in the Fah gene, which encodes the enzyme fumarylacetoacetate hydrolase. Only the host hepatocytes are defective for the Fah gene; the transplanted hepatocytes are wild type. Hence, only the host hepatocytes undergo cell death due to lack of the hydrolase. Accordingly, the transplanted hepatocytes have a growth advantage and repopulate the degenerated liver. Using this system, Overturf report that donor Fah-positive cells represent >80% of the cells

present in repopulated liver at 8-10 weeks following transplantation (see page 268, first column, lines 31-33).

Accordingly, contrary to the Examiner's position, at the time the invention was made, one of ordinary skill in the art would have found it predictable that methods other than creation of a homozygous uPA mouse could be used to cause liver degeneration in a mouse.

(iii) The Examiner alleges that, as the host range of hepatitis viruses is limited, it is unpredictable if all the hepatitis viruses recited in the claims can infect all hepatocytes recited in the claims. Here, however, the claims are clearly limited to transplanted hepatocytes that can be infected with a compatible hepatitis virus. "Compatible" is clearly defined in the specification as "any virus which is capable of replicating and developing in the xenogenic mammalian hepatocytes" (page 8, line 35 through page 9, line 1). Examples of mammalian compatible hepadnavirus and hepatocyte combinations are given in the specification in Table 1 (page 9). The references cited by the Examiner further demonstrate the advanced state of the art of hepadnavirology. The ordinarily skilled artisan would readily have access to information describing which hepatitis viruses are capable of infecting which mammalian hepatocytes. That is, which combinations are compatible, as claimed. There can be no question of unpredictability or a need for undue experimentation to practice the present claims when the required information set forth in the rejection by the Examiner is readily available in well known texts.

Finally, to support an allegation of unpredictability in practicing the claims, the Examiner contends that hepatitis E can only infect humans (see Office Action at page 7). Purcell (Hepatitis E Virus, in *Fields Virology, Third Edition,* Fields et al. (eds)., pp. 2831-2836, 1996) discloses, however, that "Primates found to be susceptible to HEV include Old World species

such as chimpanzees, macaques..., and African green monkeys; and New World species such as marmosets (tamarins), owl monkeys, and squirrel monkeys" (see page 2835). Purcell also discloses that pigs and mice have also been reported to be susceptible to infection with HEV (see page 2836).

Finally, claims 15, 17-20 and 22 are rejected under 35 U.S.C. § 112, first paragraph because the Examiner contends that the specification does not support infection of hepatocytes with viruses other than hepatitis viruses. In response, claim 15 has been amended to recite that xenogenic mammalian hepatocytes are infected with a mammalian hepatitis virus. Each of the other claims depends, either directly or indirectly from claim 15.

(iv) The Examiner has rejected claims 25-36 under 35 U.S.C. § 112 as it is allegedly unpredictable if all hepatitis viruses will transform hepatocytes resulting in HCC. This rejection is respectfully traversed. One of ordinary skill in the art could readily determine the combination of transplanted xenogenic hepatocyte and compatible virus encompassed by the claims. The specification discloses that, following the procedures prescribed in the specification to obtain a transgenic mouse transplanted with xenogenic mammalian hepatocytes infected with a compatible hepatitis virus, the skilled artisan need only prepare standard H & E stained liver sections to identify precancerous altered hepatic foci (AHF; see specification at page 27, lines 12-27). Accordingly, given the simplicity of the techniques required, it would not require undue experimentation to determine which combinations of transplanted hepatocytes and compatible hepatitis virus could be used to practice claims 25-36.

In summary, the foregoing remarks establish that the amended claims are fully enabled by the specification. Accordingly, Applicants respectfully request reconsideration of

claims 1-36 and withdrawal of all rejections of claims 1-36 under 35 U.S.C. §112, first paragraph.

IV. Rejections Under 35 U.S.C. §112, Second Paragraph

(i) Claim 14 is rejected for use of the term "derived". In response, claim 14 (and claims 23 and 35) has been amended by deleting the word "derived". The claims are now directed to a method wherein the source of xenogenic hepatocytes is a woodchuck. Accordingly, it is respectfully submitted that amended claim14 is definite. Reconsideration of claim 14 and removal of the present rejection is requested.

(ii) Claims 1, 5, 7, 8, 12, 15, 19, 21, 25, 33 and 35 are rejected as indefinite for use of the term "compatible". Claims 2-4, 6, 9-11, 13-14, 16-18, 20, 22-24, 26-32, 34 and 36 are rejected because they depend from claims 1, 8, 15 and 25. The Examiner first alleges that the term does not have a clear meaning with regard to a hepatitis virus infecting a hepatocyte. Applicants traverse on the grounds that a "compatible" virus is unambiguously defined in the specification as "any virus which is capable of replicating and developing in the xenogenic mammalian hepatocytes" (page 8, line 36 through page 9, line 1). The Examiner also contends that the specification only discusses infection of hepatocytes with species-specific hepatitis viruses. Applicants traverse on grounds that Table 1 of the specification (at page 9) sets forth both "Natural Hosts" and "Other Hosts and Cells to be Infected" for several different hepatitis viruses. Accordingly, the specification teaches that an "Other Host" for human hepatitis B virus is chimpanzee; an "Other Host" for woodchuck hepatitis virus is ground squirrel; and an "Other Host" for ground squirrel hepatitis virus is woodchuck.

The specification also discloses that an "Other Host" for human hepatitis B virus is baboon. The specification's disclosure that baboon is a host for hepatitis B virus is confirmed by Kedda et al. (Transplantation, 69:1429-1434, 2000; submitted with the Information Disclosure Statement filed concurrently herewith).

Finally, in rejecting the claims as indefinite, the Examiner states that "it is clear that the infectivity of hepatitis viruses is species specific". In response, it is noted that the references cited by the Examiner include numerous examples of hepatitis viruses that will infect a plurality of species. Hollinger et al., for example, (Hepatitis A Virus in *Fields Virology, Third Edition,* Fields et al. (eds), pp.735-752) disclose that human hepatitis A produces disease in multiple species comprising both Old World and New World monkeys (see page 751); Robinson (Hepadniviridae and their Replication, in Fields et al., *Fundamental Virology*, Second edition, 1991, see page 735) discloses that human hepatitis B virus can infect chimpanzees and a few other primates (page 990, bottom col. 1); Purcell (Hepatitis E Virus, in *Fields Virology, Third Edition,* Fields et al. (eds)., pp. 2831-2836, 1996) discloses that Old World and New World monkey, pigs, and mice are susceptible to infection with HEV (see pages 2835-2836). Thus, there can be little doubt that "compatible", as defined in the specification and as this term would be interpreted by one of ordinary skill in the art, is not (and should not be) limited to species-specific viral infection.

For the reasons set forth above, Applicants submit that claims 1, 5, 7, 8, 12, 15, 19, 21, 25, 33 and 35 meet the structures of the second paragraph of 35 U.S.C. §112. Reconsideration of the claims and withdrawal of all rejections under 35 U.S.C. §112, second paragraph is requested.

V. Rejections Under 35 U.S.C. § 102

Claims 1-5, 8-12, 15-21, 24, 25-33 and 36 are rejected under 35 U.S.C. § 102 (e) as anticipated by Kay et al., U.S. Patent No. 5,980,886. Applicants traverse on the grounds that Kay fails to provide a disclosure that would enable one of ordinary skill in the art to make and use the instantly claimed invention.

The test for anticipation is whether, "each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference" or prior public use. *Constant v. Advanced Micro-Devices, Inc.* 848 F.2d 1560, 1570 (Fed. Cir.), *cert denied*, 488 U.S. 892 (1988); *Minnesota Mining and Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.* 976 F.2d 1559, 1565 (Fed. Cir. 1992); *In re Schreiber,* 128 F.3d 1473, 1477 (Fed. Cir. 1997).

In order for a reference to be available under §102 as a prior art reference, it also must "enable" what it discloses. *In re Donohue*, 766 F.2d 531, 533 (Fed Cir 1985), 207 U.S.P.Q. 196 (CCPA 1980); 1 D. Chisum, Patents §3.04, at 3-19 (1980); 1 Deller's Walter on Patents §60 (2d ed. 1964). Thus, prior art under §102 must sufficiently describe the claimed invention to have placed the public in possession of it. *In re Sasse*, 629 F.2d 675, 681 (CCPA 1980), 207 U.S.P.Q. 107; *see also Reading & Bates Construction Co. v. Baker Energy Resources Corp.*, 748 F.2d 645, 651-652, 223 U.S.P.Q. 1168 (Fed Cir 1984). Possession is effected if one of ordinary skill in the art could have combined the description of the prior art with their own knowledge to produce the claimed invention. *In re Grice*, 301 F.2d at 939, 133 U.S.P.Q. 365 (CCPA 1962). Therefore, even if the invention is disclosed in a publication, that disclosure is not available as prior art if it was not enabling. *In re Borst*, 345 F.2d 851, 855, *cert denied.*, 382 U.S. 973, 145

U.S.P.Q. 554 (CCPA 1965).

In its broadest embodiment, the present invention comprises the steps of creating an immunetolerant mouse deficient in T and B cells which has a degenerated liver, and then repopulating the degenerated liver with xenogenic mammalian hepatocytes that are capable of being infected, either before or after transplantation, with at least one compatible mammalian hepatitis virus (see new claims 37 and 38).

The disclosure of Kay, however, fails to enable one of ordinary skill in the art to make the disclosed animal. Specifically, Kay fails to disclose any method or procedure that would enable one of ordinary skill in the art to repopulate the degenerated liver of an immunetolerant mouse with xenogenic mammalian hepatocytes that may serve as a host, i.e., be infected with, hepatitis virus. Kay most certainly offers no direct guidance as to the procedures to be used in the allegedly disclosed method for transplanting human hepatocytes into the degenerated liver of an immunetolerant mouse. Kay, for example, offers no guidance as to:

(i) what type of human hepatocytes (e.g., primary cells or cultured cells) are to be transplanted,

(ii) the number of cells to be transplanted,

(iii) the age or specific genotype of the immunodeficient mouse,

(iv) the conditions that should be used to cause liver degeneration in an immunetolerant mouse or what percentage of the liver is, or should be, degenerated prior to transplantation, and

(v) what level or over what period of time the modified, non-secreted uPA transgene disclosed in Kay should be expressed in the immunetolerant mouse to cause liver

degeneration prior to transplantation of human hepatocytes.

Kay, in summary, offers no useful guidance whatsoever as to the methods that can be used to repopulate a degenerated liver with any type of xenogenic hepatocyte (no less a xenogenic mammalian hepatocyte that is permissible for hepatitis virus infection). This is evident, as all of the procedures and Examples disclosed in Kay are related to direct transfection of hepatocytes in vivo using viral vectors. Kay gives no Examples or useful methods for transplanting hepatocytes of any kind.

Nor would any other reference available prior to the instant inventors' disclosure enable one of ordinary skill in the art to make the instantly claimed invention.

In contrast to the disclosure in Kay, the present inventors discovered methods for repopulating a degenerated liver in an immunetolerant transgenic mouse with xenogenic mammalian (woodchuck) hepatocytes. These hepatocytes are a permissible host for hepatitis virus infection. The inventors published their methods in Petersen et al. (Proc. Natl. Acad. Sci. USA 95:310-315, 1998). The methods were unknown to those of ordinary skill in the art prior to the publication of Petersen et al. The methods are the basis for the enabling disclosure presented in the instant specification.

Hence, the instant specification discloses that liver degeneration is effected by genetic transmission of a uPA transgene (opposed to viral transfection of the uPA transgene, as disclosed in Kay); the instant specification discloses that the wild type uPA transgene be used to effect liver degeneration (opposed to use of the modified uPA transgene disclosed in Kay); the instant specification discloses by reference the specific procedure for isolating the woodchuck hepatocytes that are used for transplantation, which resulted in hepatocyte viability of ≥95%

(Kay fails to provide any guidance for isolating xenogenic hepatocytes to be used in transplantation); the instant specification discloses that uPA/RAG-2 transgenic mice were 10- to 18-days old at the time of transplantation, that from 5×10^5 to 1×10^6 hepatocytes were transplanted, and that transplantation was accomplished by intrasplenic injection (Kay provides no specific guidance on transplantation of xenogenic hepatocytes into an immunetolerant mouse and offers only general limited guidance for transplantation of homologous, cultured hepatocytes).

In summary, neither the methods disclosed in Kay, nor the methods generally available to one of ordinary skill in the art would enable the skilled artisan to make and use the instant invention. Only Applicants' research established methods for practicing the instant invention. These methods were only available to those of ordinary skill in the art upon publication of the inventors' work in Petersen et al., which is not available as a reference against the instant claims.

Hence, at the time the invention was made, neither the disclosure of Kay, nor any other information available to one of ordinary skill in the art, would have enabled one of ordinary skill in the art to make and use the invention of claims 1-5, 8-12, 15-21, 24, 25-33 and 36. Kay, therefore, cannot anticipate these claims. Applicants therefore respectfully request reconsideration and withdrawal of all rejections of claims 1-5, 8-12, 15-21, 24, 25-33 and 36 under 35 U.S.C. 102 (b).

VI. Rejections Under 35 U.S.C. § 103

Claims 1-5 and 8, 9, 11 and 12 have been rejected as obvious over the combination of Rhim et al. (Proc. Natl. Acad. Sci. USA 92:4942-4946, 1995) and Vierling, U.S.

Patent No. 6,034,297. Claims 6, 10 and 13 have been rejected as obvious over Rhim and Vierling and further in view of Alt et al., U.S. Patent No. 5,583,278. Claims 7 and 14-36 have been rejected over Rhim, Vierling, Alt and further in view of Roggendorf (Intervirology 38:100-112, 1995).

In response, Applicants submit herewith a declaration of inventor Dr. Charles E Rogler, under 37 C.F.R. §1.131. The Rogler declaration reports that Dr. Rogler and co-inventor Dr. Joerg Petersen conceived and completed the instant invention in the United States prior to September 26, 1997, the filing date of the Vierling patent.

The declaration states that Dr. Rogler and Dr. Petersen conceived and carried out experiments on development of a mouse model to investigate host and viral mechanisms for determining hepadnaviral persistence and hepatocarcinogenesis. Prior to the filing date of the Vierling patent, the inventors reduced to practice a method for creating an immunetolerant mouse with liver degenerated liver, repopulating the degenerated liver with xenogenic mammalian hepatocytes that are a host for hepatitis virus, and infecting the transplanted hepatocytes with a compatible hepatitis virus cause persistent infection. The Rogler declaration also reports that, prior to the filing date of the Vierling patent, Dr. Rogler and Dr. Petersen also conceived and reduced to practice methods of using the aforementioned transgenic mouse as a model for precancerous and malignant phenotypes of the transplanted infected hepatocytes and conceived of the use of the model to study mechanisms of viral persistence in the absence of B and T cell mediated immune responses, viral replication, antiviral compounds and hepatocarcinogenesis.

The declaration further states that the aforementioned methods and experiments were described in a paper that the co-inventors authored (Petersen et al., Proc. Natl. Acad. Sci. USA 95:310-315, 1998) that was received for review on August 22, 1997, which pre-dates the September 26, 1997 filing date of the Vierling patent.

Hence, the co-inventors conceived and diligently reduced the instant invention to practice prior to the filing date of the Vierling patent. Furthermore, the Vierling patent was issued after the application date for the instant invention. Accordingly, Applicants respectfully submit that all rejections based, either in whole or in part on the Vierling patent should be withdrawn. All rejections of claims 1-36 under 35 U.S.C. § 103 depend, in part, on the Vierling patent. Applicants respectfully request reconsideration and withdrawal of all rejections of claims 1-36 under 35 U.S.C. § 103, accordingly.

The present declaration under 37 C.F.R. § 1.131 is submitted without conceding any applicability of the cited references. *Credle v. Bond*, 25 F.3d 1566, 1577-1578, 30 USPQ2d 1911, 1920-1921 (Fed. Cir. 1994). This declaration has also been submitted in co-pending application Serial No. 09/662,202, of which Drs. Rogler and Petersen are also co-inventors.

CONCLUSION

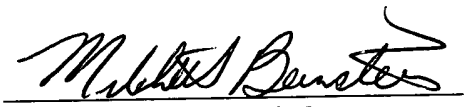
Applicants respectfully request entry of the above amendments and remarks.

The prior art of record does not suggest or disclose the present claims.

In view of the above amendments and remarks, and the accompanying declaration, this application is believed to be in condition for allowance, which is earnestly solicited.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Charles E. ROGLER et al.

Serial No.: 09/344,189

Art Unit: 1632

Filed: June 24, 1999

Examiner: P. Paras, Jr.

For: **CHRONIC HEPATITIS VIRUS INFECTION AND CLONAL HEPATOCELLULAR CARCINOMA IN MOUSE REPOPULATED LIVERS**

MARK-UP FOR AMENDMENT OF SEPTEMBER 7, 2001 PURSUANT TO 37 C.F.R. § 1.121

September 7, 2001

IN THE CLAIMS

1. (Twice amended) A method of making a chimeric mouse, comprising:

a. creating an immunetolerant mouse which has a degenerated liver and which is deficient in T and B cells; and

b. transplanting xenogenic mammalian hepatocytes to repopulate the parenchyma of the degenerated liver, said xenogenic mammalian hepatocytes being infected with at least one compatible mammalian hepatitis virus.

8. (Twice amended) A chimeric mouse model system for hepatitis comprising an immunetolerant mouse deficient in T and B cells having a degenerated liver parenchyma repopulated with transplanted xenogenic mammalian hepatocytes, said xenogenic mammalian hepatocytes infected with a compatible mammalian hepatitis virus.

14. (Amended) The chimeric mouse model system of claim 13, wherein the source of the xenogenic mammalian hepatocytes is [derived from] a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

15. (Amended) A method for screening a test compound for anti-viral activity, comprising:

a. administering said test compound to an immunetolerant chimeric mouse deficient in T and B cells which has a degenerated liver parenchyma repopulated with transplanted xenogenic mammalian hepatocytes and wherein the xenogenic mammalian hepatocytes are infected with at least one compatible mammalian hepatitis virus; and

b. assaying the level of replication of the virus.

23. (Amended) The method of claim 22, wherein the source of the xenogenic mammalian hepatocytes is [derived from] a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).

25. (Amended) A method for screening a test compound for anti-cancer activity, comprising:

a. administering said test compound to an immunetolerant chimeric mouse deficient in T and B cells which has degenerated liver parenchyma repopulated with transplanted xenogenic mammalian hepatocytes and wherein the xenogenic mammalian hepatocytes are infected with at least one compatible mammalian hepatitis virus; and

b. assaying the mice for the development of hepatocellular carcinoma in said mice.

35. (Amended) The method of claim 33, wherein the source of the xenogenic mammalian hepatocytes is [derived from] a woodchuck and the compatible mammalian hepatitis virus is Woodchuck Hepatitis Virus (WHV).